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**Initial REMS Approval: 06/01/10**

**Most Recent Modification: 05/2015**

**BL 125320 PROLIA<sup>®</sup> (denosumab)**

Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
805-447-1000

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**1. Goals**

The goal of the PROLIA<sup>®</sup> REMS is to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions by:

- a. informing healthcare providers and patients about the risks of (1) hypocalcemia, (2) osteonecrosis of the jaw, (3) atypical femoral fractures, (4) serious infections, and (5) dermatologic reactions associated with PROLIA<sup>®</sup>
- b. informing healthcare providers they should counsel patients about the risks associated with PROLIA<sup>®</sup>.

**2. REMS Elements**

**2.1 Medication Guide**

Amgen will ensure the PROLIA<sup>®</sup> Medication Guide is distributed in accordance with 21 CFR 208.24.

The [Medication Guide](#) is part of the REMS and is appended.

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## 2.2 Communication Plan

Amgen will implement the following communication plan to healthcare providers likely to prescribe PROLIA<sup>®</sup>. The communication plan will include:

### 2.2.1 REMS Letters

Amgen will send a [REMS Letter for Healthcare Providers](#) and [REMS Letter for Professional Societies](#) within 60 calendar days of this REMS modification and again 1 year after approval of this REMS modification. The REMS Letters will address potential risks of (1) hypocalcemia, (2) osteonecrosis of the jaw, (3) atypical femoral fractures, (4) serious infections, and (5) dermatologic reactions associated with PROLIA<sup>®</sup>.

The [REMS Letter for Healthcare Providers](#) will be distributed by US mail. If the [REMS Letter for Healthcare Providers](#) is undeliverable, Amgen will use available resources to obtain updated address information and send a second letter via US mail within 45 calendar days of return. If the correct address cannot be obtained, the attempt will be documented and no further communication will occur.

The [REMS Letter for Professional Societies](#) will be sent as an attachment to an email. If the email is undeliverable or marked as unopened, a second email will be sent within 7 calendar days. If the second email is undeliverable or marked as unopened, the REMS letter will be mailed within 30 calendar days.

A copy of, or a link to, the Prescribing Information (PI) and [Medication Guide](#) will accompany each REMS Letter.

### REMS Letter for Healthcare Providers

The intended audience for the [REMS Letter for Healthcare Providers](#) will be endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, and urologists.

The [REMS Letter for Healthcare Providers](#) will also be available via a link from the [PROLIA<sup>®</sup> REMS website](#), through Amgen's Medical Information Department, and from Amgen's sales and/or medical representatives upon request for one year after the approval of this REMS modification (05/2015).

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## **REMS Letter for Professional Societies**

Amgen will send the [REMS Letter for Professional Societies](#) to the following professional societies and organizations requesting the letter or its content be provided to their membership.

- National Osteoporosis Foundation
- American Society of Bone Mineral Research
- American College of Rheumatology
- American Association of Clinical Endocrinologists
- American Academy of Family Physicians
- Endocrine Society
- American Society of Clinical Oncology
- North American Menopause Society

### **2.2.2. Patient Counseling Toolkit**

Amgen will provide healthcare providers with a Patient Counseling Toolkit, including a [Patient Counseling Chart for Healthcare Providers](#), a [Patient Brochure](#), and copies of the PI and [Medication Guide](#). Throughout the duration of the REMS, the contents of the Patient Counseling Toolkit will be detailed to targeted healthcare providers (eg, endocrinologists, rheumatologists, obstetricians/gynecologists, primary care physicians, oncologists, urologists) where Amgen has sales representatives deployed to speak with healthcare providers in the field. These targeted healthcare providers include prescribers who are likely to prescribe PROLIA®.

### **Patient Counseling Chart for Healthcare Providers**

Amgen will provide a [Patient Counseling Chart for Healthcare Providers](#), which will be a standalone tool for healthcare providers to counsel patients. Amgen sales or medical representatives will verbally discuss the risk messages contained in the [Patient Counseling Chart for Healthcare Providers](#) during the visit with the healthcare provider.

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## **Patient Brochure**

The [Patient Brochure](#) includes information on risk messages and will be provided to healthcare provider offices as an additional counseling tool for patients.

### **2.2.3. Journal Information Piece**

Amgen will publish a [journal information piece](#) quarterly for 12 months after approval of the REMS modification (05/2015) in the following professional journals:

- Journal of the American Medical Association
- Arthritis and Rheumatology
- Endocrine Today

### **2.2.4. Dissemination of REMS Information at Scientific Meetings**

The PROLIA<sup>®</sup> REMS Patient Counseling Toolkit will be prominently displayed at relevant scientific meetings where Amgen has a PROLIA<sup>®</sup> commercial booth presence for the duration of the REMS.

### **2.2.5. REMS Website**

The [PROLIA<sup>®</sup> REMS website](#) for healthcare professionals ([www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy)) will continue for the duration of the REMS. The REMS website will include the option to print versions of the PI, [Medication Guide](#), [REMS Letter for Healthcare Providers](#), [Patient Counseling Chart for Healthcare Providers](#), [Patient Brochure](#), and [journal information piece](#). The PROLIA<sup>®</sup> product website will include a prominent REMS-specific link to [PROLIA<sup>®</sup> REMS website](#). All website information will be updated within 60 days post approval of the modification.

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The following are part of the PROLIA<sup>®</sup> REMS and are appended:

- [REMS Letter for Healthcare Providers](#)
- [REMS Letter for Professional Societies](#)
- [Patient Counseling Chart for Healthcare Providers](#)
- [Patient Brochure](#)
- [Journal Information Piece](#)
- [REMS Website \(landing page\)](#)

### **3. Timetable for Submission of Assessments**

Amgen will submit REMS Assessments to FDA at 18 months, 3, 6, and 7 years from the date of the initial approval (01 June 2010) of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Amgen will submit each assessment so that it will be received by the FDA on or before the due date.

**MEDICATION GUIDE**  
**Prolia® (PRÓ-lee-a)**  
**(denosumab)**  
**Injection, for subcutaneous use**

Read the Medication Guide that comes with Prolia before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Prolia.

**What is the most important information I should know about Prolia?**

If you receive Prolia, you should not receive XGEVA®. Prolia contains the same medicine as Xgeva (denosumab).

**Prolia can cause serious side effects including:**

- **Serious allergic reactions.**

Serious allergic reactions have happened in people who take Prolia. Call your doctor or go to your nearest emergency room right away if you have any symptoms of a serious allergic reaction. Symptoms of a serious allergic reaction may include:

- low blood pressure (hypotension)
- trouble breathing
- throat tightness
- swelling of your face, lips, or tongue
- rash
- itching
- hives

- **Low calcium levels in your blood (hypocalcemia).**

Prolia may lower the calcium levels in your blood. If you have low blood calcium before you start receiving Prolia, it may get worse during treatment. Your low blood calcium must be treated before you receive Prolia. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia. Take calcium and vitamin D as your doctor tells you to.

- **Severe jaw bone problems (osteonecrosis).**

Severe jaw bone problems may happen when you take Prolia. Your doctor should examine your mouth before you start Prolia. Your doctor may tell you

to see your dentist before you start Prolia. It is important for you to practice good mouth care during treatment with Prolia. Ask your doctor or dentist about good mouth care if you have any questions

- **Unusual thigh bone fractures.**

Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture include new or unusual pain in your hip, groin, or thigh.

- **Serious infections.**

Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia. Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia. You may need to go to the hospital for treatment if you develop an infection.

Prolia is a medicine that may affect the ability of your body to fight infections. People who have weakened immune system or take medicines that affect the immune system may have an increased risk for developing serious infections.

Call your doctor right away if you have any of the following symptoms of infection:

- Fever or chills
  - Skin that looks red or swollen and is hot or tender to touch
  - Fever, shortness of breath, cough that will not go away
  - Severe abdominal pain
  - Frequent or urgent need to urinate or burning feeling when you urinate
- **Skin problems.**  
Skin problems such as inflammation of your skin (dermatitis), rash, and eczema may happen if you take Prolia. Call your doctor if you have any of the following symptoms of skin problems that do not go away or get worse:
    - Redness
    - Itching
    - Small bumps or patches (rash)
    - Your skin is dry or feels like leather
    - Blisters that ooze or become crusty
    - Skin peeling
  - **Bone, joint, or muscle pain.**  
Some people who take Prolia develop severe bone, joint, or muscle pain.

**Call your doctor right away if you have any of these side effects.**

## What is Prolia?

Prolia is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause (“change of life”) who:
  - are at high risk for fracture (broken bone)
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body

It is not known if Prolia is safe and effective in children.

## Who should not take Prolia?

### Do not take Prolia if you:

- have been told by your doctor that your blood calcium level is too low.
- are pregnant or plan to become pregnant
- are allergic to denosumab or any of the ingredients in Prolia. See the end of this leaflet for a complete list of ingredients in Prolia.

## What should I tell my doctor before taking Prolia?

### Before taking Prolia, tell your doctor if you:

- Are taking a medicine called Xgeva (denosumab). Xgeva contains the same medicine as Prolia.
- Have low blood calcium
- Cannot take daily calcium and vitamin D
- Had parathyroid or thyroid surgery (glands located in your neck)
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Have kidney problems or are on kidney dialysis
- Plan to have dental surgery or teeth removed.
- Are pregnant or plan to become pregnant. Prolia may harm your unborn baby. Tell your doctor right away if you become pregnant while taking Prolia.
  - **Pregnancy Surveillance Program:** Prolia is not intended for use in pregnant women. If you become pregnant while taking Prolia, talk to your doctor about enrolling in Amgen’s Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN). The purpose of this program is to collect information about women who have become pregnant while taking Prolia.
- Are breastfeeding or plan to breastfeed. It is not known if Prolia passes into your breast milk. You and your doctor should decide if you will take Prolia or breastfeed. You should not do both.



**Tell your doctor about all the medicines you take**, including prescription and nonprescription drugs, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of medicines with you to show to your doctor or pharmacist when you get a new medicine.

### **How will I receive Prolia?**

- Prolia is an injection that will be given to you by a healthcare professional. Prolia is injected under your skin (subcutaneous).
- You will receive Prolia 1 time every 6 months.
- You should take calcium and vitamin D as your doctor tells you to while you receive Prolia.
- If you miss a dose of Prolia, you should receive your injection as soon as you can.
- Take good care of your teeth and gums while you receive Prolia. Brush and floss your teeth regularly.
- Tell your dentist that you are receiving Prolia before you have dental work.

### **What are the possible side effects of Prolia?**

Prolia may cause serious side effects.

- See **“What is the most important information I should know about Prolia?”**
- It is not known if the use of Prolia over a long period of time may cause slow healing of broken bones.

The most common side effects of Prolia in women who are being treated for osteoporosis after menopause are:

- back pain
- pain in your arms and legs
- high cholesterol
- muscle pain
- bladder infection

The most common side effects of Prolia in men with osteoporosis are:

- back pain
- joint pain
- common cold (runny nose or sore throat)

The most common side effects of Prolia in patients receiving certain treatments for prostate or breast cancer are:

- joint pain
- back pain
- pain in your arms and legs
- muscle pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Prolia. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Prolia if I need to pick it up from a pharmacy?**

- Keep Prolia in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton.
- Do not freeze Prolia.
- When you remove Prolia from the refrigerator, Prolia must be kept at room temperature [up to 77°F (25°C)] in the original carton and must be used within 14 days.
- Do not keep Prolia at temperatures above 77°F (25°C). Warm temperatures will affect how Prolia works.
- Do not shake Prolia.
- Keep Prolia in the original carton to protect from light.

**Keep Prolia and all medicines out of reach of children.**

**General information about Prolia.**

Do not give Prolia to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Prolia. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Prolia that is written for health professionals.

For more information, go to [www.Prolia.com](http://www.Prolia.com) or call Amgen at 1-800-772-6436.

**What are the ingredients in Prolia?**

Active ingredient: denosumab

Inactive ingredients: sorbitol, acetate, polysorbate 20 (prefilled syringe only), Water for Injection (USP), and sodium hydroxide



Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, California 91320-1799

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Revised: 02/2015



## PROLIA<sup>®</sup> REMS

# FDA Required REMS Safety Information

### Serious Risks Associated with Prolia<sup>®</sup> (denosumab)

- Hypocalcemia
- Osteonecrosis of the Jaw
- Atypical Femoral Fractures
- Serious Infections
- Dermatologic Reactions

Month YYYY

## Important Safety Update

Dear Healthcare Provider:

The FDA has required this safety update as part of the PROLIA<sup>®</sup> REMS (**R**isk **E**valuation and **M**itigation **S**trategy) to inform healthcare providers about the following **serious risks of Prolia<sup>®</sup>**:

### Hypocalcemia

- Hypocalcemia may be exacerbated by the use of Prolia<sup>®</sup>.

### Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Prolia<sup>®</sup>.

### Atypical Subtrochanteric and Diaphyseal Femoral Fractures

- Atypical low-energy or low trauma subtrochanteric and diaphyseal femoral fractures, which may be bilateral, have been reported in patients receiving Prolia<sup>®</sup>. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area.

### Serious Infections

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia<sup>®</sup> presented with serious infections, such as serious skin infection and endocarditis, leading to hospitalization more frequently than the placebo group.

### Dermatologic Reactions

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia<sup>®</sup> presented with generalized epidermal and dermal adverse events at a significantly higher rate compared to the placebo group. These included dermatitis, eczema, and rashes.

## Role of the Healthcare Provider

- ✓ **Make note** of these risks and discuss them with your patients using the non-promotional **Patient Counseling Toolkit**, which includes:

- **Patient Counseling Chart for Healthcare Providers**
- **Patient Brochure**
- **Prescribing Information**
- **Medication Guide**

Note: these materials are available to order through 1-800-77-AMGEN (1-800-772-6436), by downloading the information from [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy), or by contacting your local Amgen Sales Representative.

- ✓ **Review** information in the **Medication Guide and Patient Counseling Chart** with your patients, including the serious risks of Prolia® and the symptoms of each risk.
- ✓ **Advise** each patient to seek prompt medical attention if they have signs or symptoms of any of the serious risks.
- ✓ **Provide** each patient a copy of the **Medication Guide** and **Patient Brochure**.
- ✓ **Visit** [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy) for more information about the Prolia® REMS.

## Indication

Prolia® is a RANK ligand (RANKL) inhibitor indicated for the:

- 1) treatment of postmenopausal women with osteoporosis at high risk for fracture,
- 2) treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- 3) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and
- 4) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

**This letter does not contain the complete safety profile for Prolia®. Please review the Prescribing Information and Medication Guide, enclosed.**

## Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia® to the FDA or to Amgen at 1-800-772-6436.

Sincerely,

Isma Benattia, MD  
Vice President, Global Patient Safety  
Amgen

[Attachment of the Prolia® Prescribing Information and Medication Guide]



## PROLIA<sup>®</sup> REMS

### FDA Required REMS Safety Information

#### Serious Risks Associated with Prolia<sup>®</sup> (denosumab)

- Hypocalcemia
- Osteonecrosis of the Jaw
- Atypical Femoral Fractures
- Serious Infections
- Dermatologic Reactions

Month YYYY

### Important Safety Update

Dear [Professional Society]:

The FDA has required Amgen to distribute this safety update to your organization as part of our PROLIA<sup>®</sup> REMS (**R**isk **E**valuation and **M**itigation **S**trategy) program. We request that you inform your members about the following **serious risks of Prolia<sup>®</sup>**:

#### **Hypocalcemia**

- Hypocalcemia may be exacerbated by the use of Prolia<sup>®</sup>.

#### **Osteonecrosis of the Jaw**

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Prolia<sup>®</sup>.

#### **Atypical Subtrochanteric and Diaphyseal Femoral Fractures**

- Atypical low-energy or low trauma subtrochanteric and diaphyseal femoral fractures, which may be bilateral, have been reported in patients receiving Prolia<sup>®</sup>. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area.

#### **Serious Infections**

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia<sup>®</sup> presented with serious infections, such as serious skin infection and endocarditis, leading to hospitalization more frequently than the placebo group.

#### **Dermatologic Reactions**

- In a clinical trial, women with postmenopausal osteoporosis treated with Prolia<sup>®</sup> presented with generalized epidermal and dermal adverse events at a significantly higher rate compared to the placebo group. These included dermatitis, eczema, and rashes.

## Role of the Healthcare Provider

- ✓ **Make note** of these risks and discuss them with your patients using the non-promotional **Patient Counseling Toolkit**, which includes:

- [Patient Counseling Chart for Healthcare Providers](#)
- [Patient Brochure](#)
- [Prescribing Information](#)
- [Medication Guide](#)

**Note:** These materials are available to order through 1-800-77-AMGEN (1-800-772-6436) or by downloading the information from [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy).

- ✓ **Review** information in the **Medication Guide and Patient Counseling Chart** with each patient, including the serious risks of Prolia® and the symptoms of each risk.
- ✓ **Advise** each patient to seek prompt medical attention if they have signs or symptoms of any of the serious risks.
- ✓ **Provide** each patient a copy of the **Medication Guide** and **Patient Brochure**.
- ✓ **Visit** [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy) for more information about the Prolia® REMS.

## Indication

Prolia® is a RANK ligand (RANKL) inhibitor indicated for the:

- 1) treatment of postmenopausal women with osteoporosis at high risk for fracture,
- 2) treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- 3) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and
- 4) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

**This letter does not contain the complete safety profile for Prolia®. Please visit [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy) for more information about Prolia® and the Prolia® REMS Program. A link to the full Prescribing Information is provided where risks associated with Prolia® are clearly outlined.**

## Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia® to the FDA or to Amgen at 1-800-772-6436.

Sincerely,

Isma Benattia, MD  
Vice President, Global Patient Safety  
Amgen

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# Prolia<sup>®</sup> (denosumab): Patient Counseling Chart for Healthcare Providers

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# Prolia® (denosumab): What Patients Need to Know

# What side effects can Prolia® (denosumab) have?

## What is Prolia®?

Prolia® is a prescription medicine used to:

- Treat osteoporosis in women after menopause who:
  - are at high risk for fracture
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body

Prolia® can cause serious side effects including:

- Low calcium levels in your blood (see page 4)
- Severe jaw bone problems (osteonecrosis) (see page 5)
- Unusual thigh fractures (see page 6)
- Serious infections (see page 7)
- Skin problems (see page 8)

Please talk about these side effects with your doctor.

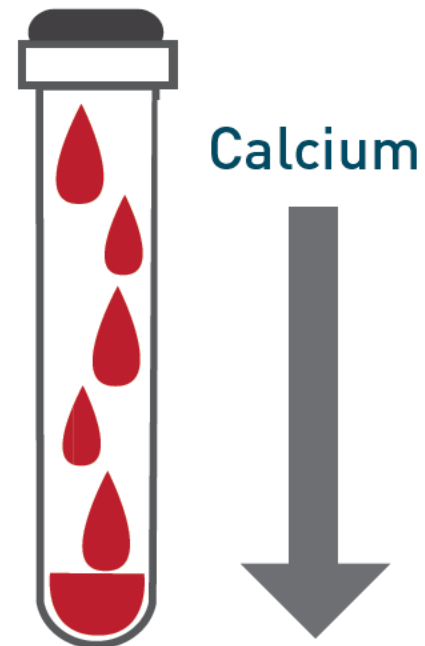


Call your doctor right away if you think you may be having any of these side effects.



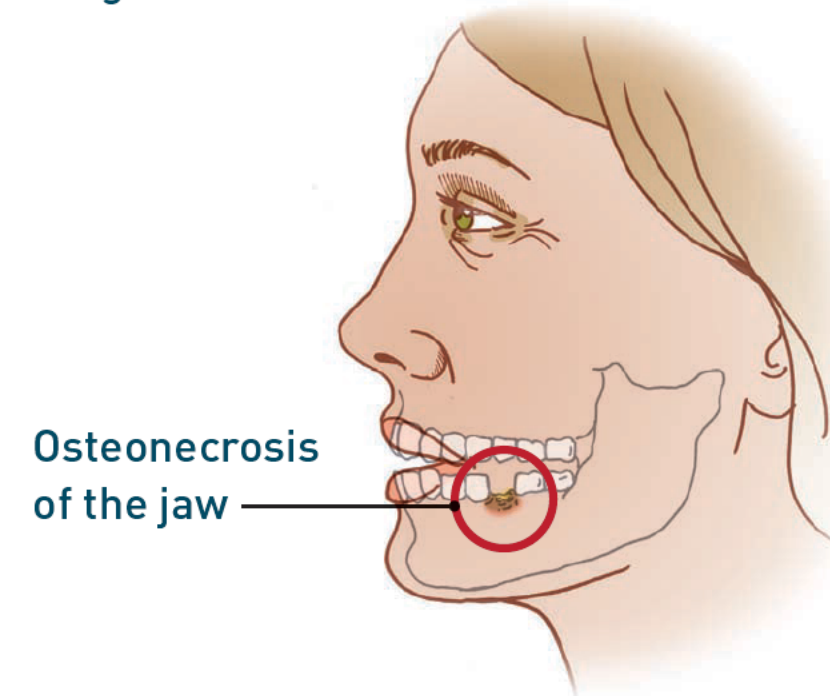
## Low calcium levels in your blood

- Prolia® may lower the calcium levels in your blood
- Symptoms of low blood calcium include:
  - Spasms, twitches, or cramps in your muscles
  - Numbness or tingling in your fingers, toes, or around your mouth
- If you have low blood calcium before you start receiving Prolia®, it may get worse during treatment
- Your low blood calcium must be treated before you receive Prolia®
- Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia®. Take calcium and vitamin D as your doctor tells you to



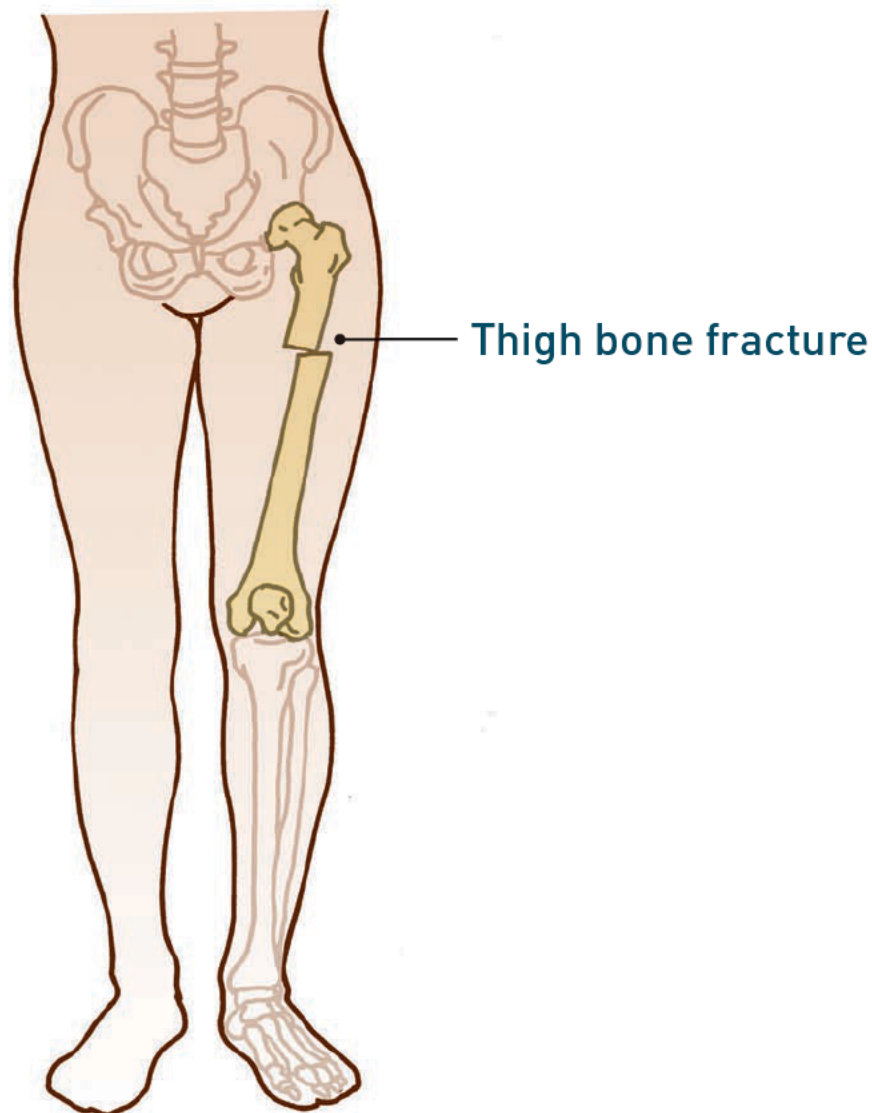
## Severe jaw bone problems (osteonecrosis)

- Severe jaw bone problems (osteonecrosis of the jaw or ONJ) may happen when you take Prolia®
- ONJ is a potentially serious condition that can be seen as a sore in the mouth through which the jaw bone is sometimes visible. The jaw bone and gum tissue over the bone may heal slowly or not heal at all
- The most common risk factor associated with ONJ is tooth extraction. It is important for you to practice good mouth care during treatment with Prolia®
- See your dentist regularly for check-ups and cleaning
- Tell your dentist you are taking Prolia® or will start taking Prolia®



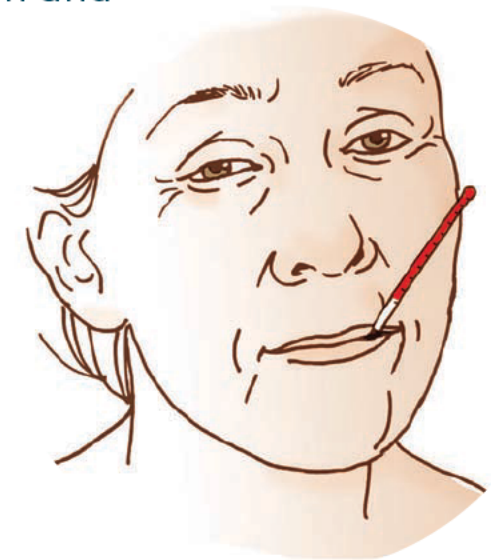
# Unusual thigh fractures

- Some people have developed unusual fractures in their thigh bone
- Symptoms of thigh bone fracture include new or unusual pain in your hip, groin, or thigh



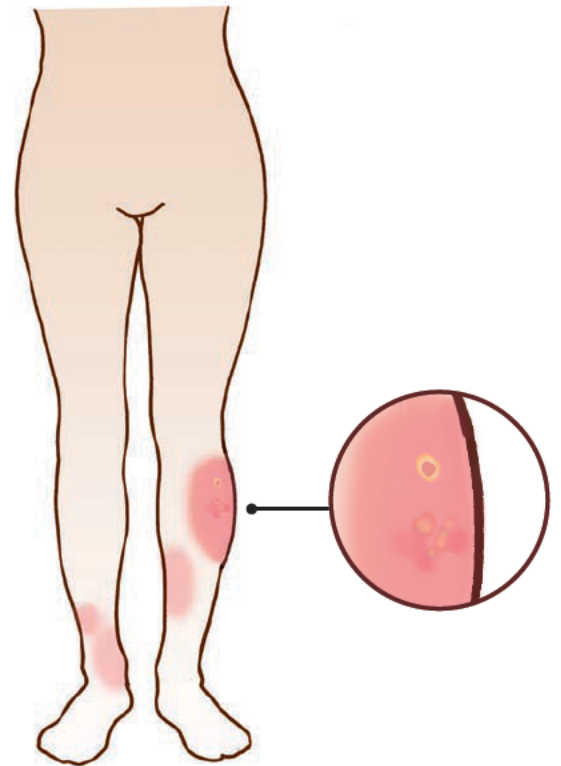
# Serious infections

- Prolia® is a medicine that may affect the ability of your body to fight infections
- Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia®
- Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia®
- Symptoms of some serious infections include:
  - Fever or chills
  - Skin that looks red or swollen and is hot or tender to touch
  - Fever, shortness of breath, cough that will not go away
  - Frequent or urgent need to urinate or burning feeling when you urinate



# Skin problems

- Skin problems may happen if you take Prolia®
- Symptoms of skin problems include:
  - Dermatitis (redness, itching)
  - Eczema (leathery dry skin, blisters that ooze or become crusty, skin peeling)



Call your doctor right away if you think you may be having any of these side effects.



Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
[www.amgen.com](http://www.amgen.com)  
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# Prolia® (denosumab) Guide for Patients: Important Things YOU Need to Know

## What is Prolia®?

Prolia® is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause (“change of life”) who:
  - are at high risk for fracture (broken bone)
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body

## What side effects can Prolia® have?

Prolia® can cause serious side effects that all patients taking Prolia® must know.

Please talk about these side effects with your doctor.

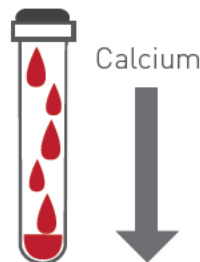


Call your doctor right away if you think you may be having any of these side effects.

The side effects can include:

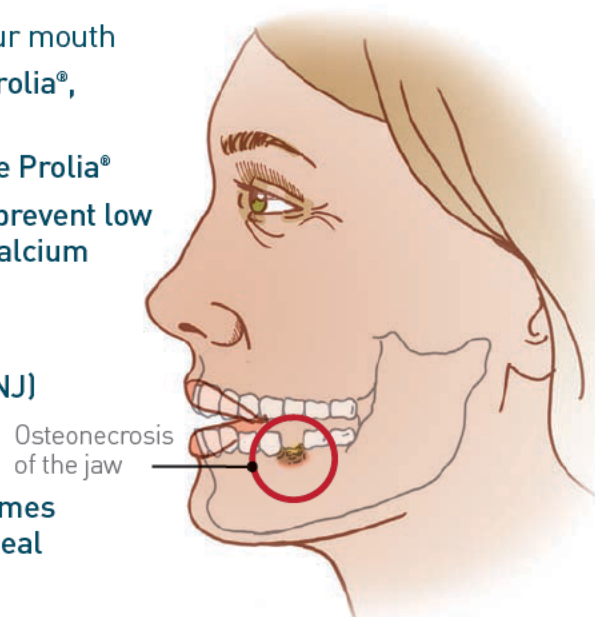
### Low calcium levels in your blood

- Prolia® may lower the calcium levels in your blood
- Symptoms of low blood calcium include:
  - Spasms, twitches, or cramps in your muscles
  - Numbness or tingling in your fingers, toes, or around your mouth
- If you have low blood calcium before you start receiving Prolia®, it may get worse during treatment
- Your low blood calcium must be treated before you receive Prolia®
- Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia®. Take calcium and vitamin D as your doctor tells you to



### Severe jaw bone problems (osteonecrosis)

- Severe jaw bone problems (osteonecrosis of the jaw or ONJ) may happen when you take Prolia®
- ONJ is a potentially serious condition that can be seen as a sore in the mouth through which the jaw bone is sometimes visible. The jaw bone and gum tissue over the bone may heal slowly or not heal at all



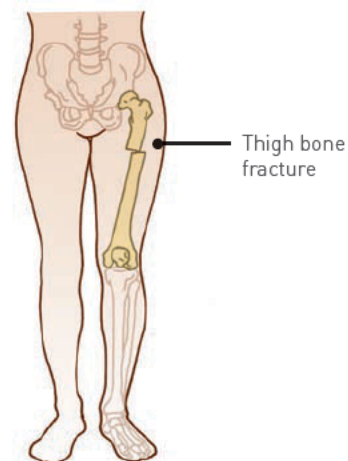
Side effects are continued on back.

### Severe jaw bone problems (osteonecrosis) cont.

- The most common risk factor associated with ONJ is tooth extraction.  
It is important for you to practice good mouth care during treatment with Prolia®
- See your dentist regularly for check-ups and cleaning
- Tell your dentist you are taking Prolia® or will start taking Prolia®

### Unusual thigh fractures

- Some people have developed unusual fractures in their thigh bone
- Symptoms of thigh bone fracture include new or unusual pain in your hip, groin, or thigh



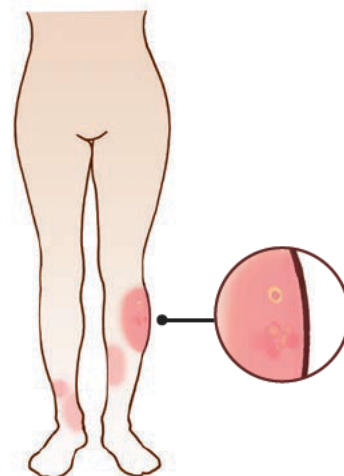
### Serious infections

- Prolia® is a medicine that may affect the ability of your body to fight infections
- Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia®
- Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia®
- Symptoms of some serious infections include:
  - Fever or chills
  - Skin that looks red or swollen and is hot or tender to touch
  - Fever, shortness of breath, cough that will not go away
  - Frequent or urgent need to urinate or burning feeling when you urinate



### Skin problems

- Skin problems may happen if you take Prolia®
- Symptoms of skin problems include:
  - Dermatitis (redness, itching)
  - Eczema (leathery dry skin, blisters that ooze or become crusty, skin peeling)



**Call your doctor right away if you think you may be having any of these side effects.**



Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
www.amgen.com  
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# FDA REQUIRED REMS Safety Information for Prolia® (denosumab)

## Serious Risks Associated with Prolia®:

### Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of Prolia®. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended.

### Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving Prolia®. ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing.

### Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical low-energy or low trauma subtrochanteric and diaphyseal femoral fractures, which may be bilateral, have been reported in patients receiving Prolia®. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area.

### Serious Infections

In a clinical trial, women with postmenopausal osteoporosis treated with Prolia® presented with serious infections, such as infections of the abdomen, urinary tract, and ear, as well as endocarditis.

### Dermatologic Reactions

In a clinical trial, women with postmenopausal osteoporosis treated with Prolia® presented with generalized epidermal and dermal adverse events at a significantly higher rate compared to the placebo group.

## Role of the Healthcare Provider

- ✓ **Review** information in the Prolia® Medication Guide and Patient Counseling Chart with each patient, including the serious risks of Prolia® and the symptoms of each risk.
- ✓ **Advise** each patient to seek prompt medical attention if they have signs or symptoms of any of the serious risks.
- ✓ **Provide** each patient a copy of the Medication Guide and Patient Brochure.

## Prolia® is Indicated for the:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

### Reporting Adverse Events

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia® to the FDA or to Amgen at 1-800-772-6436.

*This journal information piece is part of the FDA-required Prolia® REMS. Visit [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy) for more information.*

*For complete safety information, see the Prescribing Information available at [www.proliahcp.com/risk-evaluation-mitigation-strategy](http://www.proliahcp.com/risk-evaluation-mitigation-strategy).*



# ***Prolia® (denosumab) Risk Evaluation and Mitigation Strategy***

## **What is the Prolia® REMS?**

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the Food and Drug Administration to manage known or potential serious risks associated with a drug product.

The purpose of the Prolia® REMS is to inform healthcare providers and patients about the following serious risks of:

- ▶ Hypocalcemia
- ▶ Osteonecrosis of the jaw
- ▶ Atypical femoral fractures
- ▶ Serious infections
- ▶ Dermatologic reactions

The Prolia® REMS program materials are designed to inform healthcare providers and patients about these risks with Prolia®. They include a REMS Letter for Healthcare Providers, Patient Counseling Chart for Healthcare Providers, Patient Brochure, Journal Information Piece, Prescribing Information, and Medication Guide. It is important that you discuss with your patients the information included in the Patient Counseling Chart for Healthcare Providers, the Patient Brochure, and the Medication Guide.

**To learn more about the serious risks of Prolia®, read the [Important Safety Information](#) provided in this link and use the links on the right to access REMS supporting materials.**

## **Reporting Adverse Events**

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088. Healthcare providers should report all suspected adverse events associated with Prolia® to the FDA or to Amgen at 1-800-772-6436.

### **Materials for Healthcare Providers**

 [REMS Letter for Healthcare Providers ▶](#)

 [Journal Information Piece ▶](#)

#### **Patient Counseling Toolkit**

 [Patient Counseling Chart for Healthcare Providers ▶](#)

 [Patient Brochure ▶](#)

 [Prescribing Information ▶](#)

 [Medication Guide ▶](#)

### **Materials for Patients**

 [Patient Brochure ▶](#)

 [Medication Guide ▶](#)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTINE P NGUYEN  
05/21/2015